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REPORT OF THE INTERNATIONAL PLAGUE CONFERENCE.

Held at Mukden, April, 1911, under the auspices of the Chinese Government.

Edited by ERICH MARTINI, G. F. PETRIE, ARTHUR STANLEY, AND RICHARD P. STRONG.

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The Bureau of Science of the Government of the Philippine Islands has been appointed sole agent for the distribution of the printed proceedings of the International Plague Conference.

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THE PHILIPPINE

JOURNAL OF SCIENCE

B. THE PHILIPPINE JOURNAL OF
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A STUDY OF POLYNEURITIS GALLINARUM.[1] A FIFTH CONTRIBUTION TO THE ETIOLOGY OF BERIBERI.

By EDWARD B. VEDDER and ELBERT CLARK.[2]

CONTENTS.[3]

Since Eijkman (1) first described polyneuritis gallinarum a large number of investigators have studied this disease. At the present time there is general agreement among these investigators that the disease is produced by an exclusive diet of polished rice and may be prevented and cured by the addition of rice polishings or various extracts of rice polishings to the diet. Some of these investigators (2) (3) (4) described briefly the symptomatology and pathology of the disease, but the majority have confined themselves to the study of its etiology.

[1] Read before the Philippine Islands Medical Association, November, 1912, and published with permission of the Chief Surgeon, Philippine Division.

[2] Edward B. Vedder, captain, Medical Corps, United States Army, member of the United States Army Board for the Study of Tropical Diseases as they Exist in the Philippine Islands.

Elbert Clark, associate professor of anatomy, University of the Philippines.

[3] The experimental work is by Vedder; the microscopic work by Clark.

In a series of experiments lasting for several years and reported elsewhere, (5) (6) (7) (8) we have had an excellent opportunity to study polyneuritis gallinarum and therefore believe that our observations on its symptomatology and pathology may be of value. In addition, we have made observations which throw an entirely new light on the pathology of this interesting disease.

I. OBSERVATIONS ON SYMPTOMATOLOGY.

Incubation period.—Observers agree that, when fowls are fed exclusively on polished rice, the symptoms of polyneuritis appear in from twenty to thirty days. We have a record of 124 fowls in which the conditions of the experiment were such as to permit an accurate observation of the period of incubation. The average incubation period of the disease in these fowls was 26.86 days. The shortest incubation period observed was seventeen days, but a number of cases occurred in eighteen and nineteen days. On the other hand, in a number of cases the disease only appeared after forty days. These fowls were all fed on polished rice. However, if fowls are fed on a diet of polished rice, but receive in addition small amounts of other foodstuffs, or an amount of extract of rice polishings which is insufficient to afford complete protection, they suffer from the disease in its typical form, but only after a greatly prolonged incubation period. Thus, some of our fowls on such a diet have developed neuritis after ninety days' feeding, and Eijkman records a case where neuritis appeared only after a year's feeding.

Percentage of fowls affected.—Of 211 fowls on an exclusive diet of polished rice, 154, or 73 per cent, have developed polyneuritis while 57, or 27 per cent, have not shown any symptoms of the disease. The experiments from which this observation is made continued for only sixty days. It is, of course, probable that a higher percentage of fowls would have succumbed if the experiments had been extended over a longer period.

Course of the disease.—A typical case of the disease may be described as follows. Careful observation during the incubation period will reveal nothing abnormal, except that the fowl may be noticed standing bunched up with ruffled feathers and the comb may become blue. The first symptom noticed is a weakness of the legs, so that the fowl is unable to walk well, and as he steps there is a tendency for the joint formed by the tibio-tarsus and the tarso-metatarsus to give way, causing the fowl to sink to the ground. This is due to beginning paralysis of the extensor muscles of the leg which, it will be remembered, are the first

muscles to be affected in men suffering from beriberi. A peculiarity in the gait may be recognized before the legs become completely paralyzed. This is a tendency to raise the feet high in the air and thrust forward with them as though the fowl were attempting to brush away something. This high-stepping gait has never been seen in any condition affecting fowls other than polyneuritis. The fowl may show a tendency to teeter forward on its toes, and may stumble when hurried. From the time when paralysis first appears the disease progresses with great rapidity, and as a rule by the second day the fowl will be unable to stand. The position assumed by the bird in this condition is very characteristic. Usually it sits quite still upon its flexed tarso-metatarsus, but occasionally a bird of more vigor attempts to walk about the cage. However, as the extensor muscles are completely paralyzed, it can not walk upon its feet, but shuffles along upon its flexed tarso-metatarsus. The paralysis now extends rapidly cephalad affecting the muscles of the wings, the neck, and the body, usually in the order named. As a result, the bird is soon unable to sit up, but lies upon its side. There seems, however, to be a general weakness or debility associated with this paralysis. At any rate, the fowl becomes prostrated rather more rapidly than one would expect as a result of mere muscular paralysis. Most of the fowls affected in this way die very promptly, and it is by no means unusual to find the bird dead within two or three days after the first onset of the disease. Some fowls live longer, but almost none survive for a week after the paralysis has set in.

Wing drop.—Many of the birds present this symptom, which consists in inability to hold the wings in the accustomed position close to the body. They droop in some cases until the wing feathers trail on the ground. This symptom, which is probably due to the paralysis of the wing muscles referred to above, does not occur in all cases and comes on later than the leg symptom. It will be remembered that beriberi in man almost always commences by affecting the muscles of the legs, and if the arms are affected this is almost always during a later stage of the disease.

Spasticity.—This occurs in rare instances during the development of the disease, but more often during recovery. A fowl that has developed this spastic gait stands and walks with the knees stiff, leaning forward on the tips of the toes so that the ball of the foot scarcely touches the ground. In the effort to maintain its balance, short rapid steps are taken as though the body were so far forward that the feet have to hurry to keep up. During walking the feet frequently strike together and,

when the spasticity is severe, the fowl topples forward as the result of this interference of the legs.

Retraction of the head.—This is a frequent symptom in the later stage of the disease. The anterior groups of muscles in the neck become paralyzed, and the continued action of the posterior groups retracts the head far backward. This overbalances the fowl so that it is unable to sit upon its paralyzed legs. If a fowl in this condition is placed upon its legs in a squatting position, it makes several spasmodic efforts to retain its equilibrium, and finally topples over backward. Such a fowl is unable to rise without help.

Dysphagia.—After the fowl becomes so paralyzed that it is unable to arise, dysphagia almost always sets in. The fowl appears to be totally unable to swallow normally, and when water or medicines are administered they run out of the mouth when the bird is laid down, unless care is exercised to prevent this. It is also very easy to choke such a bird by attempting to revive it by hand feeding.

Respiration.—The respiration of the fowl suffering from an advanced stage of the disease is slower and deeper than normal. As the bird lies on its side, its abdomen may be observed to expand and contract slowly almost like a pair of bellows.

Sensory symptoms.—It is somewhat difficult to obtain accurate information with regard to the sensory changes. But by tapping, pinching, and pricking the legs, and comparing the reaction with that obtained in normal fowls, it is apparent that sensation is much reduced in the legs of birds suffering from polyneuritis, and it is believed that this loss of sensation precedes slightly the motor paralysis. It is possible that the peculiar high-stepping gait described above may be the result of sensory disturbance.

Loss of weight.—Progressive loss of weight was an almost constant symptom. Thus of 20 fowls fed on polished rice, whose weights were carefully recorded, the average weight at the beginning of the experiment was 3.15 pounds. The average weight of these same fowls taken on the date when the first symptoms of polyneuritis appeared was 2.45 pounds. This represents an average loss of 0.7 pound, or 22 per cent, of their original body weight. A few fowls, however, developed neuritis although they lost comparatively little weight. Thus one fowl whose original weight was 3 pounds 1 ounce developed neuritis after a loss of only 3 ounces, and several fowls lost only 5 ounces.

This loss of weight is such a constant observation, that the view has been held that polyneuritis of fowls is simply the result of inanition which is expressed by this loss of weight. That this

is not the case is shown by the fact that fowls fed on polished rice and protected by an extract of rice polishings also lose weight but do not develop neuritis. Thus 25 fowls fed in this way, of an average original weight of 3.08 pounds, weighed 2.68 pounds at the conclusion of the experiments which lasted ninety days. They thus lost an average of 0.4 pound, or 13 per cent, of their original weight as compared with the 22 per cent lost by the fowls on the same diet but which received no protection. Moreover, several fowls in this group ended the experiment with no loss of weight, and one or two fowls actually gained a few ounces.

Fulminating cases.—While the disease, as described above, appears to be the usual form, a certain percentage of cases present marked variations. Some of the cases are even more rapid in their course, and for lack of a better name may be called fulminating cases. During the incubation period they may lose considerable weight and may appear to be in poor health, but they rarely show any paralysis of the legs. They will be seen in this condition on one day, and the next day will be found lying on the side completely prostrated, often with the neck retracted, and exhibiting the characteristic breathing already described. Death follows within a few hours. The course of the disease in these cases is therefore much more rapid, and is marked by much greater muscular wasting and general prostration than usual.

In a still smaller percentage of cases, paralysis of the legs occurs suddenly as already described, but the bird remains in good general health. The comb is red, the appetite remains good, and the fowls lose little weight. We have had several fowls that lived in this paralyzed state, but in good health otherwise, for a month while still subsisting upon polished rice.

Treatment.—Fowls affected with any of these forms of polyneuritis can rarely be saved by feeding an ordinary mixed diet. Almost all die in spite of efforts to save them by hand feeding. But if they are given an extract of rice polishings, the majority of them can be saved. A great difference, however, has been observed in the manner in which fowls respond to this treatment. Thus birds affected with the form of the disease described as fulminating have been observed that appeared moribund, but recovered almost completely after the administration of this extract, so that they were able to walk about within a few days. This result has not been obtained with fowls suffering from marked paralysis. If birds of this latter group are given this extract, they improve in general health, but the paralysis remains, and it is usually only after several months of treatment that they recover complete control of their legs.

The relation between the amount of polished rice eaten and the development of neuritis.—It has been generally observed that the great majority of the fowls fed on polished rice usually lose their appetites after about a week on this diet, and thereafter eat only small amounts of rice. There are always a few fowls, however, which eat greedily up to the very last, and will eat far greater amounts than the usual ration allowed (120 grams). Several deductions have been drawn from this fact with regard to the development of neuritis. Some observers have thought that those fowls that have eaten well throughout the experiment have been protected from the development of the disease by this increased consumption of rice and, therefore, have been inclined to regard polyneuritis as the result of simple inanition. On the other hand, other observers have thought that those fowls that ate the most rice developed the disease soonest, and have regarded this as an argument in favor of the theory that polyneuritis is caused by some toxin contained in the polished rice. We have observed fowls that always ate well, and yet developed neuritis sooner than usual; we have observed other fowls that ate large quantities of rice throughout the experiment, but whose incubation period was longer than normal. Again, some of the fowls that have eaten poorly have developed neuritis promptly, while others have not developed the disease at all. Therefore, it is believed that the amount of rice eaten has little to do with the development of the disease, which depends rather on the idiosyncrasy of the fowl with regard to the amount of neuritis-preventing substance required.

II. OBSERVATIONS ON PATHOLOGY.

Eijkman, Fraser and Stanton, Chamberlain and Vedder, and others have described degeneration in the sciatic nerves of the domestic fowl after a prolonged diet on polished rice. The questions as to whether the condition is a general nervous affection or a peripheral neuritis, as to the extent of the degenerative changes, the selective localization of the affection, the place of onset of the neuritis and regeneration have led us, in addition to what has been said above, into a study of the minute anatomical changes which may take place in the nervous system in such fowls.

A microscopic study was first made of those nervous elements in which the degenerative changes are probably first manifested and in which these changes are most apparent, that is, the peripheral nerves. This, as might well be expected, increased our interest in the more obscure changes.

In considering in this connection the general question of polyneuritis, it is natural to inquire whether the neuritis is peripheral or involves the entire nervous system. The neuritis produced in fowls by a prolonged diet of polished rice is, so far as the best evidence indicates, a neuritis due to a deficiency of some food constituent or constituents necessary for the maintenance of the metabolic and functional activity of the nervous system. The numerous feeding experiments noted above and the experience and results of Eijkman, Fraser and Stanton, Chamberlain and Vedder, and others well-nigh place this hypothesis beyond the pale of doubt. This being granted, it is probable that the neuritis is, in a greater or lesser degree, a general systematic affection—greater or lesser, because one would not expect different animals to react similarly to any given etiological factor.

The observation that some of our fowls show prostration without showing any well-marked symptoms of peripheral neuritis is evidence favoring the theory of a general nervous affection. This prostration comes on suddenly. It is extremely difficult to bring about recovery after the severest prostration. On the other hand, fowls show varying degrees of peripheral neuritis in the legs while maintaining otherwise good systemic conditions. As many cases come under this latter class, and as the affection often appears to be distinctly limited to the legs in these fowls, we are justified in saying that, whatever the state of the general nervous system, the disease shows a great tendency to involve the peripheral nerves. However, certain observations on the ganglia cells, the nerve cells of the lumbosacral cord, and the anatomical changes in the fiber tracts of the cord and the brain stem itself have convinced us that the central nervous system is much more involved than has been generally thought.

In those cases where the affection is selective enough to be termed peripheral neuritis, one naturally inquires whether it is a primary or a secondary affection; that is, whether the degeneration of the fibers of the peripheral nerve precedes or follows changes in the nerve cells of these fibers. From our present knowledge of the degeneration of nerves, there is little difficulty in supposing that the degeneration in the fibers may be primary, secondary to, or simultaneous with, degenerative changes in their nerve cell. For we know on the Wallerian theory that a fiber severed from its cell or deprived of the "tropic" influence of the cell undergoes degeneration. And, on the other hand, in a cell thus separated from its nerve fiber, atrophic changes occur from disuse.

Some claim that degeneration in the sciatic nerve in beriberi begins in the most peripheral rami, in the smaller branches of the lower part of the leg and foot, and proceeds centrally. These observers claim that the large sciatic nerve shows degeneration at a later period than its peripheral and smaller rami and that at any given time the degeneration in a small peripheral ramus is relatively greater and further advanced than in the fibers of the sciatic in the upper thigh region and precedes any changes in the nerve cells. Were these observations confirmed and proved beyond doubt for polyneuritis in the fowl, the question of the primary affection would be settled. On such a theory of peripheral neuritis we would not expect to find degenerative changes in fiber tracts of the cord and the higher nerve centers. At most, degenerative changes in the fiber tracts of the cord would follow only after atrophic changes in the cells of the dorsal root ganglia and of the ventral horn of gray matter had advanced to a considerable degree. Since, as Engelmann (9) has shown, in a sectioned nerve "in the central stump, despite its functional inactivity, no further changes (*i. e.*, beyond the first node of Ranvier) occurred for months," we should scarcely expect to find degenerative changes in the fiber tracts of the cord (aside from those fibers running between the nerve cells and the periphery of the cord) during at least the first two months of the experiment. This, however, does not agree with our observations which show degenerative changes in the fiber tracts of the cord and changes in its nerve cells. In view of the fact that fowls die shortly after symptoms of neuritis manifest themselves, which circumstance occurs in most cases before the thirtieth day of the experiment and rarely later than forty days, it would seem that degeneration in the cord—on the above hypothesis, a degeneration of disuse—would not be expected. We were not able to confirm the assumption, as will be shown, that degeneration begins in and is more extensive in the most peripheral fibers.

Our microscopic study comprises:

A. Pathology.
1. Changes in the heart.
2. Degenerative changes in the peripheral nerves including the vagus.
3. Degenerative changes in the nerve roots.
4. Changes within the fiber tracts of the cord and brain.
5. Changes in the nerve cells of the cord and dorsal root ganglia.
6. Regeneration.

B. Time of onset of degeneration in peripheral nerves.

Changes in the heart.—Following our own observations that in those fowls showing symptoms of peripheral neuritis or prostration the vagus showed a greater or less degree of degenerative change, an examination was made of the heart. In the gross, the heart showed little or no change from normal. Hypertrophy was not observed. There was an absence or diminution of fat beneath the pericardium. In most cases the myocardium was of a lighter hue than normal. Pericardial fluid was never present in great excess. Aside from those cases of extreme prostration before death, œdema was not noticed. In some of these latter cases a slight œdema was observed beneath the pericardium at the base of the heart. Microscopically, in the hearts of those fowls dead after prostration there was little to be observed which would indicate a pathological change in the musculature. A few fibers here and there were seen in the myocardium of the ventricles in which the cross striation was more or less obscure and which stained poorly. An apparent increase in pigment was also noted in several hearts. At most, we would hesitate to claim any changes further than those which would indicate beginning parenchymatous or mucoid degeneration. In those fowls which presented chiefly the symptoms of peripheral neuritis it was even more difficult to observe changes which could be considered pathological, and in some cases no change whatever was to be noted.

Degeneration in the peripheral nerves. The vagus.—Degenerative changes, as shown by the Marchi method, were observed in all the cases examined. Plate III, figs. 5 and 6, illustrates high- and low-power photomicrographs of a vagus nerve showing degeneration stained by Marchi's method. Unlike the sciatic nerve, however, the extent and degree of degeneration in the vagus did not always correspond to the severity of the symptoms before death, nor was the most extensive degeneration to be seen in the vagus nerve of those cases which showed prostration. Fowls in good general condition sometimes showed extensive degeneration in the vagus. Likewise, we were not able to establish an interrelation between the severity of the degeneration in the vagus and the amount of pathologic change in the heart.

That there may be no interrelation between the severity of nervous symptoms and the systemic condition of the animal before death on the one hand and the degree or extent of degeneration found in the vagus nerve on the other is well shown by the following four cases:

Fowl 3 showed symptoms of very little peripheral neuritis

(slight indications of paralysis), but became suddenly prostrated. The vagus nerve showed almost no degeneration.

Fowl 5 showed extreme peripheral neuritis, no prostration, and little degeneration in vagus.

Fowl 6 showed marked peripheral neuritis, no prostration, and extensive degeneration in vagus.

Fowl 8 showed marked peripheral neuritis, extreme prostration, and extensive and advanced degeneration in vagus.

The vagus nerve of fowl 13 (Plate III, fig. 5) shows the extent to which degeneration may progress in the vagus, and in our series is relatively advanced degeneration for the vagus. In the teased preparations of the vagus nerve of this fowl no single nerve fiber could be found which did not show areas of blackening along its course. This was found to obtain in the vagus of most of the cases; that is, that somewhere along its course in segments of the nerve from 2 to 5 millimeters long, each fiber showed one or more areas of blackening with the osmic acid of Marchi solution. At the periphery of this illustration single fibers may be seen showing frequent globules of fat along their course. In those vagi showing little degeneration the blackened areas are not so numerous.

Plate III, fig. 6, is a high-power view of a teased preparation of the same nerve. In this there will be seen rather large globules of degenerated myelin. This stage is about as far advanced as has been observed by us. It will be noted that, while there is a distinct globular arrangement of degenerated myelin, there is no vacuolation of either degenerated myelin or of the medullary sheath. In no case has there been observed a vacuolation of the medullary sheath nor a collection of degenerated myelin into very large globules as is found in the sciatic nerve or as is very characteristic in peripheral nerves which show Wallerian degeneration after section. There has not been observed a breaking up of the axis cylinder of the fibers of the vagus. These observations lead us to believe that, although in polyneuritis in fowls each nerve fiber of the vagus may, and usually does, show degenerative changes by the Marchi method, this degeneration never progresses far enough before the death of the fowl to bring about the destruction of the axis cylinder.

Cervical ganglion and its pre- and postganglionic fibers.—The superior and inferior cervical ganglia from several cases were examined by the Marchi method for degeneration. Very small droplets of fat, approximately one-half micron in diameter, were observed in many of the ganglia cells. However, these were by no means numerous, ranging from 4 or 5 to 20 or 30 in a cell,

but not in more than one-third of the cells. In the medullated pre- and postganglionic fibers larger, though fewer, globules of fat were seen. It was found very difficult to tease the ganglia, and sections after paraffine embedding were made. It is thus quite possible that the degeneration here observed does not represent the full extent to which degeneration had progressed in these fibers. In the nonmedullated fibers no multiplication of the nuclei of the neurilemma was observed. Thus, while there are indications of degeneration in the sympathetic ganglia (that is, cervical ganglia) and their fibers, this degeneration is slight, and a careful search must be made to detect it.

The sciatic and its peripheral branches.—Most of the investigators who have undertaken a study of polyneuritis in fowls have taken the sciatic as a basis for their anatomical study, and have confined themselves to the Marchi stain. In most cases all that was desired was to know if degeneration had or had not taken place. Thus far the Marchi method is an excellent one and well adapted for the purpose. On the other hand, to obtain an opinion as to the extent of degeneration, an indication of the probable changes which have occurred within the nerve, including the condition of the axis cylinder and nuclei of the neurilemma sheath, the Marchi method must be supplemented by other staining methods. In our study of the degenerative changes occurring in the sciatic nerve we have employed the Marchi; the Weigert stain for myelin sheath; the Altmann, the Benda, and the Meves mitochondria methods; the Golgi, Cajal, Mallory, fuchsin, and safranin methods for the axis cylinder; and hæmatoxylin methods for the nuclei of the neurilemma sheath.

As in the case of the vagus, in those sciatic nerves in which degenerative changes are apparent by the Marchi method, practically every fiber shows some indication of degeneration within short limits of its course (2 to 5 millimeters). The degenerative appearances, however, vary within the widest limits in the various fibers of the same nerve. In nerves from well-marked cases many fibers show only slight changes—small black droplets or a localized slight blackening—here and there at relatively wide intervals, from 100 to 500 microns along their course. Other fibers, and these form the majority of the fibers, show more extensive change—larger and more frequent droplets of degenerated myelin. A certain proportion of the fibers from well-marked cases of neuritis show advanced degenerative changes. These make up from 10 to 15 per cent of the fibers. Whether the other fibers show advanced degeneration at other places we could not prove beyond doubt, but regeneration experiments,

which are usually characterized by the rapid recovery of the fowl, indicate that they do not. These fibers showing advanced degeneration are marked by the accumulation of myelin in large globules and droplets, a swelling and bulging of the nerve sheath at these points, and a disintegration of the axis cylinder. The largest globules usually appear vesicular and, in their center, segments or fragments of the axis cylinder are frequently to be seen. In these larger and some of the smaller globules the stainable material is found at the periphery and appears laminated. This laminated appearance is very characteristic in Weigert preparations and is the rule in the larger globules. Usually 3 distinct layers are clearly visible of which the outer is the thickest. Other incomplete layers and fragments are seen centrally. The larger globules of degenerated myelin are not in proximity with one another; they are separated by at least many microns. The space between contains a few small droplets of degenerated myelin. It seems otherwise almost or quite devoid of structural contents. In other fibers the change appears just as complete and the segments and globules of the degenerated myelin are just as evident, but the globules are uniformly smaller. The same fiber may and probably does show both conditions at different places along its course.

Plate II, fig. 3, *b*, shows a nerve fiber in which degenerative changes are well marked. None of the largest globules are shown. Small droplets are seen between the larger globules in the otherwise apparently empty space. In this fiber the change of myelin into fat seems complete, while in fiber, *c*, the myelin seems intact and quite normal in appearance. It will be noted that here and there the degenerated myelin fails to fill the neurilemma sheath. Thus an apparently empty space is left between the latter and the degenerated myelin. This is in contrast to the condition found in those fibers containing the largest globules. Here the globule fills and distends the neurilemma.

In addition to the appearance just noted, other fibers were seen, in the nerves where degeneration was most marked, in which the degenerated myelin was confined to small droplets which failed still further of filling up the neurilemma sheath. Here segments of the axis cylinder were less frequent, but the more or less indistinct granules which were taken to be fragments of the axis cylinder were more numerous. In others the neurilemma sheath appeared much shrunken or collapsed, and a few small droplets of degenerated myelin were contained within.

A careful study of all these fibers has convinced us that the successive stages of myelin degeneration correspond pretty well with the order just described. The earliest stage made apparent by the Marchi method consists of a slight swelling of the medullary sheath, which shows a diffused blackening with the osmic acid and slight tendency toward segmentation at the circumference. Plate II, fig. 3, *a*, and Plate IV, fig. 7, show such fibers.[4]

Then follows the stage in which the largest globules distending the nerve are seen. Next is the stage in which the globules are much smaller, though quite black and discrete, and which only partly fill the sheath of Schwann. In the succeeding stage, the globules are very small but numerous. Then follows a stage where the shrunken neurilemma contains only a few scattered droplets of fat.

The neuraxis.—As stated above, the axis cylinder in those nerve fibers which show marked degeneration usually appears broken up. In the larger globules of myelin and at other places, segments of the axis cylinder were to be seen. Plate V, fig. 9, shows such a fiber. The granular appearance of the axis cylinder as is shown in this figure is quite typical for axis cylinders in fibers of this type. The segments enclosed within the globules of myelin which are usually curved or somewhat S-shaped also show this granulation when stained in certain dyes; carmine, acid fuchsin, Mallory's phosphomolybdic acid, hæmatoxylin, etc.

It might be remarked in this connection that many authors hold the view that the axis cylinder contains many neurofibrillæ along whose course many fine granules or enlargements are scattered. In those fibers in which the degeneration is further advanced, the remains of the axis cylinder is seen; not as a segmented, but rather as a fragmented structure. The fragments appear rather indistinct and diffuse and contain small obscure granules. The appearance somewhat simulates in section coagulated exudate or serum. Plate V, fig. 10, *a*, illustrates the appearance of a fragmented axis cylinder after staining with hæmatoxylin and acid fuchsin. In each fiber showing advanced myelin degeneration the axis cylinder was broken up. Segments of the axis cylinder are to be seen in all the large globules if properly stained. Whether the breaking up of the axis cylinder precedes or follows the formation of the large

[4] A diffuse blackening of the myelin, however, may be obtained even in a normal nerve by too short a mordanting in the Müller's fluid or by prolonged staining in Marchi's mixture. The tendency to segmentation though is absent.

globules must remain more or less a matter of speculation. Our observations lead us to believe that they occur somewhere near the same time.

Certain nerve fibers observed by us from nerves showing marked myelin degeneration gave indications of a segmentation of the myelin sheath and a disappearance of myelin with a persistence of the axis cylinder. This, however, has not been sufficiently confirmed to claim it as a possible type of degeneration in polyneuritis.

The neurilemma.—The neurilemma persists throughout all degenerative stages and in all fibers. No fiber was seen in which the neurilemma could not be easily distinguished. In Plate II, fig. 4, showing well-marked degeneration in a fiber of the sciatic nerve, the typical appearance of the neurilemma is well illustrated. Here the sheath of Schwann does not appear hypertrophied nor is there present an increase in the number of nuclei.

Degeneration in the proximal part of the sciatic and in its peripheral rami.—All phases of the degeneration described above for the fibers of the sciatic were to be seen in its peripheral branches and no additional type was seen. On the theory that the affection begins in the peripheral branches and progresses toward the spinal cord, one would expect to find in preparations from a given fowl more advanced and more extensive degeneration in the peripheral rami than near the spinal cord. Further, that degeneration might be found in the peripheral nerves—those supplying the foot and lower part of the leg—and not be apparent in the sciatic. Our observations do not warrant either assumption. In two teased preparations from a given nerve stained by the Marchi method, it is impossible to distinguish which is peripheral and which central. In both cases all fibers show some degeneration. As stated above, in preparations from fowls presenting well-marked symptoms of peripheral neuritis, 10 to 15 per cent of the fibers show well-marked degeneration. These are clearly differentiated from the remainder of the fibers. The number of these fibers showing marked degeneration has always been found practically the same near the cord and in the peripheral branches; thus in fowl 37, suffering from marked peripheral neuritis, in 500 fibers from different portions of the central end of the sciatic, 51, or 10.2 per cent, showed well-marked degeneration. One of the finer peripheral rami taken from near the foot contained 535 fibers of which 58, or 10.8 per cent, showed marked degeneration.

In cross sections of nerves of other fowls we found, respectively, fibers in advanced degeneration as follows:

a. Four in a total of 208 fibers in a peripheral nerve and 5 in 285 of the sciatic.

b. Five in a total of 193 fibers in a peripheral nerve and 7 in 421 of the sciatic.

c. Four in a total of 154 fibers in a peripheral nerve and 10 in 368 of the sciatic.

These figures represent advanced degeneration in one plane, and as noted above do not include all the fibers showing advanced degeneration.

We are then unable to distinguish any anatomical difference in degeneration in the central portion of the sciatic and its peripheral branches as to extent, degree, or time of onset. Thus we are of the opinion that degeneration progresses uniformly throughout the course of the fibers as has been shown to be the case in the peripheral portion of a sectioned nerve. Nor should we expect, either from the symptoms of neuritis shown by the fowl before death or from our knowledge of experimental degeneration of nerves, that in the present case degeneration would begin at the periphery and progress centrally. Within a few hours after showing the first symptoms of neuritis the fowl usually "comes down" and is unable to walk. The proximal portion of the sciatic in these fowls shows advanced degeneration.

We know from curare experiments, fatigue experiments, cold block, etc., that when a motor nerve ending is placed out of commission, the nerve itself is of no more service than if it were completely degenerated or sectioned. Stimulation by any means whatsoever produces absolutely no effect on the muscle which it supplies. Now, in polyneuritis in fowls on a polished rice diet, should degeneration progress from the periphery, the fowl would show paralysis just as soon as degeneration in the peripheral rami or in their end organs had progressed to a certain extent. This in all cases would be before degeneration to a similar degree or extent occurred in the sciatic (from which the peripheral nerves arise), and we should expect to find fowls that had just developed paralysis, in which the peripheral nerves showed advanced degeneration and whose sciatic showed only the earlier stages or none whatever. As stated above, we have not observed this condition in a single fowl. On the contrary, there are proportionately just as many nerves showing a breaking up of the axis cylinder in the sciatic as in its more peripheral rami. This, indeed, is the exact parallel of the condition in peripheral nerves showing degeneration after section as was shown by Monakow.(10)

According to this observer, degeneration in a sectioned nerve progresses uniformly throughout the peripheral part. Thus the only condition in which we should expect to find more degenerated fibers in the peripheral nerves than in the sciatic would be in the case of those fibers which branch as the periphery is approached, both rami showing degeneration.

Nerve roots.—The nerve roots in several cases were examined after staining by the Marchi as well as by the Weigert and mitochondria methods. Degeneration was observed in both ventral and dorsal roots by all these methods. However, degeneration was more frequent and much more pronounced in the ventral than dorsal roots.

Ventral roots.—Degeneration in the ventral nerve roots of the sciatic was pronounced in those cases in which degeneration in the sciatic was marked and degeneration in the two (*i. e.*, sciatic and nerve roots) was parallel and comparable; in fact, teased preparations from the ventral nerve roots resembled very closely teased preparations from the sciatic. In the ventral nerve roots degeneration was easily demonstrated by all the methods mentioned above.

Dorsal nerve roots.—In those cases in which degeneration was far advanced in the fibers of the sciatic, degeneration was demonstrated in the dorsal nerve roots. In other cases it was more difficult to demonstrate or was absent altogether. In only the most advanced cases was degeneration to be seen after the Marchi method. In other cases it required the mitochondria method to bring out the changes. Owing to the difficulty in teasing, the section method was frequently employed. The changes in the dorsal nerve roots resembled more nearly the earlier stages of degeneration in the fibers of the sciatic. Few cases were seen where advanced degeneration was present.

The spinal cord.—Degeneration within the spinal cord was observed in the fiber tracts of all columns, and changes were observed in the nerve cells of both ventral and dorsal horns.

The fiber tracts.—When a specimen of the spinal cord from a normal fowl is treated by the Marchi method, it shows in both sectioned and teased preparations numerous small black areas. In teased preparations (which are very difficult to obtain) and in cross sections of the cord, these small black areas, which are about the size of the smaller globules in a degenerated nerve, are seen in close relation with the fibers in the cord. It is sometimes difficult to tell whether a given globule is within the fiber or in apposition to it. Naturally then other methods must also be employed to confirm any suspected degeneration within the

cord. All the methods enumerated above (the Weigert and mitochondria methods) for the myelin sheath and others for the neuraxis were made use of to this end.

Plate I, fig. 2, is a photomicrograph from the anterior lateral portion of the white matter of the cord of a normal fowl after Marchi method. The black areas shown at *a* are the globules referred to, which stain black in the Marchi fluid. A careful inspection will show that these are not within the fibers, but are in close proximity to them. What these structures represent we have not determined. At *b* two fibers show enclosures which resemble very much the small droplets of myelin in a degenerated nerve fiber. These we have noted occasionally here and there, but have not interpreted them. However, despite these resemblances to degeneration of fibers in the normal cord, the picture presented by a section or a teased preparation from the cord of a fowl with well-marked paralysis is easily distinguishable as one showing degeneration.

In studying degeneration in the fibers of the spinal cord, sections and teased preparations were made from the thoracic cord. Since, as has been pointed out, the nerve roots of the sciatic group show degeneration, a preparation from the lumbosacral cord showing degeneration might indicate nothing more than degeneration in the fibers of the roots passing up or down the cord for a short distance. True degeneration in the columns of the cord would be equally apparent in the thoracic region where primary fibers of the sciatic group are absent.

Plate VI, figs. 11 and 12, and Plate VII, fig. 13, are from the thoracic cord of fowls with marked degeneration in the sciatic nerve. Fig. 13 is low-power magnification of the lateral column of the cord (as near the pyramidal tract as we could determine) of a fowl whose sciatic showed marked degeneration. At *a*, *a′*, *a″*, and *a′ ″* appearances strongly suggestive of degeneration within the fibers are seen. Owing to the fact that the fibers of the cord do not run a straight nor parallel course, it is extremely difficult, and much a matter of chance, to get a longitudinal section which shows the course of a fiber except for a short distance. Plate VI, fig. 11, a low-power magnification of the dorsomesial (Goll's) columns of the cord of another fowl with marked degeneration in the sciatic, shows at *a*, *a′*, *a″*, etc., undoubted enclosures of degenerated myelin within the fibers. Plate VI, fig. 12, is a higher magnification of a small area of the same. Whatever the other dark areas may mean, there can be little doubt that at *a* and *a′* two fibers are seen which contain

globules of degenerated myelin. This is especially evident at *a*, which gives the appearance of a globule from which much of the fat has been dissolved by the clearing agent.

It might be claimed that, since the spinal cord gives off two spinal nerves at each segment of the vertebral column, the fibers described above might represent primary fibers from the nerve roots of these spinal nerves. We recognize this as a possibility in many cases. However, it must not be forgotten that the fibers of Goll's column (ascending) are secondary neuraxes of sensory fibers which enter the cord in the lumbosacral region; that is, that they are axis-cylinder processes of cells situated in this portion of the cord. It might be further pointed out that the more mesial fibers arise from cells in the lower segments of the cord. Now, since fibers *a* and *a'*, fig. 11, are such mesial fibers, it follows that they can not be fibers of the nerve roots of the thoracic spinal nerves, but are fibers of Goll's column showing degeneration.

If the medullary sheath of the fibers within the cord shows myelin degeneration, it is natural to inquire into the state of the axis cylinder. Longitudinal and transverse sections of the thoracic region of the cord have been examined after staining by the various methods noted above for the axis cylinder. Appearances of degeneration similar to those described for the axis cylinder of certain fibers of the sciatic have been noted in the fibers of all columns of the cord. These changes consist in segmentation and fragmentation which are evident only in longitudinal sections of the cord and granulation which is best seen in transverse section. We were unable to determine whether relatively more fibers show a breaking up of the axis cylinder in one column than in another. This is due to several reasons. We have no stain distinctly specific for the axis cylinder. The Golgi, Cajal, and other metallic methods besides bringing out other structures can not be relied upon to impregnate every axis cylinder; it is very difficult to stain a degenerating axis cylinder, and small corpora amylacea and neuroglia cells with their small amount of surrounding connective tissue might easily be mistaken for cross section of such a fiber.

Plate V, fig. 10, which is from the posterior lateral column of the thoracic cord of a fowl with well-marked neuritis, shows at *a* and *a'* two fibers with degenerating axis cylinders. The axis cylinder shows a granular or somewhat flocculent appearance, and probably represents an advanced stage of degeneration. As the columns of the cord are not well demarcated, we

are not able to say whether these fibers are ascending or descending; that is, sensory or motor. The number of fibers of the cord which show undoubted degeneration in either the axis cylinder or the medullary sheath was in no case great—much less than we had expected to find. The number of the former scarcely make up 0.25 per cent of the total fibers in *a given cross section,* while the latter are approximately 1 per cent in the most advanced cases. These observations lead us to believe that in fowls showing well-marked neuritis there is degeneration in a very small percentage of the fibers of all columns of the spinal cord.

Changes in the brain.—Similar observations in Marchi preparations were made on the fiber tracts of the medulla, pons, midbrain, and internal capsule of fowl 72. Degenerated fibers were found in each one of these brain divisions comparable to those found in the cord, Plate V, fig. 23.

Changes in the nerve cells. Cells of the cord.—One would expect that degeneration in the fibers of all columns of the cord and in the peripheral nerves would be accompanied by changes in the nerve cells themselves. Our attention has been confined chiefly to a study of the cells of the lumbosacral cord. From what has been said above relative to degeneration in the peripheral nerves and in the fiber tracts of the cord, it is evident that the most marked changes in the nerve cells of the cord would be found in the lumbosacral region. For a study of these changes we have employed the Nissl method, Giemsa's blood stain after alcohol fixation, and the mitochrondria methods.

Plate X, fig. 19, shows a nerve cell from the anterior horn of the thoracic region of a normal fowl stained by Nissl's method. No nerve processes are shown. Plate X, fig. 20, is a similar nerve cell stained by Giemsa's blood stain. In both cells the tigroid substance is well shown.

In the spinal cord of the fowls showing well-marked degeneration in the sciatic, we have never been able to find a nerve cell in the lumbosacral portion, in which the tigroid substance shows as clear distinct areas like those in figs. 19 and 20. The stainable substance shows a marked tendency to diffusion throughout the cell. Cells from these cords, however, were observed in which the tigroid bodies appeared as definite though indistinct globules or areas. The usual appearance of the large cells of the anterior horn and of the large cells of the posterior horn was a diffusion of the stainable material and a collection of it at one side of the cell. The stainable material which is granular in

appearance shows a tendency to group itself around the base of one of the processes of the cell (Plate X, figs. 21 and 22), but whether this process is usually the axon as shown in fig. 22, *a*, we are not able to say. This figure shows the typical appearance of the large nerve cells of the ventrolateral horn, from which the fibers of the ventral root arise, and of the large cells of the posterior horn around which the terminations of the sensory neuraxes from the dorsal root ganglia arborize. Its granular appearance is suggestive of a disintegration rather than a solution of the tigroid substance. The cells of the other parts of the gray matter of the cord do not show this change to such an extent. They stain poorly, the stain is easily differentiated out, and the cell has a pale appearance. The stainable portions are arranged in a coarse reticular network. The appearance is that of a cell in which the tigroid substance is wanting. Cells of somewhat similar appearance are also seen in sections of the normal cord, but are not so numerous here. A comparison between the large cells of the anterior and posterior horns of the normal and neuritic fowl, noted above, is best made by a study of figs. 19 and 20 and of figs. 21 and 22. Fig. 22 gives the appearance of rather advanced retrogressive changes. The stainable material is collected at one point of the cell and causes a bulging here. The nucleus also suggests degenerative changes. This has been noted in very few cells, and the picture is the most suggestive of degeneration in the nerve cells of any we have seen.

Since marked changes in the tigroid substance of the nerve cells of the spinal cord can be brought about, as Nissl(11) and others have shown, by fatigue, direct electrical stimulation in excess, toxemia, and other factors, it is impossible to say that the changes noted in the nerve cells of the neuritic fowls represent degenerative changes or changes due to other causes. We have thus employed other methods in studying these cells. By the Marchi method a few very fine, intensely black granules can be seen here and there within the nerve cell. These, however, are so scarce that their pathologic significance is probably very small. A study of the mitochondria of the nerve cells was next made.

Of recent years a great deal of work has been devoted to the study of mitochondria and their significance. Mitochondria occur as numerous rods and granules in all the various types of cells of the embryo (Bensley,(12) Meves,(13) and others) and in practically all types of cells of the adult, which have an active metabolism or which are actively engaged in secretion, as the

numerous researches of Meves, Benda,(14) Bensley, Regaud,(15) Renaut, and others have shown. For the great advance which has been made in our knowledge of this subject, we are probably justified in saying that mitochondria are identical with the "Filarmasse" of Flemming, the "Bioblasts" of Altmann,(16) (Meves, Bensley, and others), and are necessary for the metabolic and functional activity of the cell. Regaud and others have shown that mitochondria occur in normal nerve cells and Cowdry(17) and others have shown that they are distinct from the tigroid substance and that the two occur simultaneously in the same normal nerve cell. One of us (Clark) has not been able to demonstrate them in certain pathologic cells (pancreas). An examination of the nerve cells of the spinal cord of the fowls with marked degeneration in the sciatic nerve by the mitochondria method shows rods and granules in cells of the type which show such marked changes by the Nissl method. In the cells of the thoracic cord it was practically impossible to distinguish between the cells from the normal and from the neuritic fowl as regards mitochondria. The rods and granules were perhaps a little less numerous in the latter cells, but this is far from being definite. A cell with no mitochondria was not observed in the lumbosacral cord of the more advanced cases.

We are thus of the opinion that, along with degeneration in the peripheral nerves and in the fiber tracts of the cord, there occur changes in certain nerve cells of the anterior and posterior horns of the spinal cord, which may or may not signify degenerative changes, but which probably never progress to any great extent before death of the fowl.

Regeneration.—In the numerous experiments to bring about recovery after prostration or after pronounced symptoms of peripheral neuritis had manifested themselves, we have found that fowls show as much individual variation here as they do in developing the affection. Of fowls in which the symptoms were distinctly those of peripheral neuritis (severe in nearly all), recovery was accomplished in almost every case.

The nerves from fowls, carried toward recovery by feeding for sixty days and which were apparently well, were examined for degeneration. In a majority of the fibers only very small blackened areas (Marchi's method) were to be seen. From 10 to 15 per cent of the fibers, however, showed segmentation and globular arrangement of the myelin and no axis cylinder. The globules were never large at this period, and the core of the fiber within the neurilemma sheath contained relatively large amounts

of apparently empty space. This appearance is strongly suggestive of a partial absorption of the large globules of degenerated myelin seen in the nerves of fowls with marked peripheral neuritis. These observations make it probable that regeneration in those nerves showing advanced degeneration is very slow or doubtful, that recovery after neuritis means a recovery of those nerve fibers which do not show advanced degenerative processes, and that in recovery after peripheral neuritis the fowl is able to do without the 10 or 15 per cent of the fibers which are the slowest to regenerate. Rapid regeneration after prostration alone confirms the anatomical findings that degeneration is further advanced in the nerves of those fowls showing symptoms of peripheral neuritis than prostration without peripheral neuritis.

III. OBSERVATIONS ON THE EARLIEST DEGENERATIVE CHANGES IN THE NERVES.

Time of onset of degenerative changes in the fibers of the sciatic nerve.—Finding that degenerative changes were to be observed in the sciatic nerve of all those fowls which had been on a polished rice diet for thirty-five days or more, even though symptoms of neuritis did not manifest themselves (Plate XI, fig. 24), we sought to determine when the first changes are to be detected. From the advanced degeneration occurring in some fibers of such nerves, it became evident that degenerative changes took place long before signs of neuritis were evident. It became an interesting point to determine at what period these degenerative changes are first to be detected. Accordingly 12 fowls were fed polished rice and killed at varying intervals of time, ranging from seven to twenty-three days. Thus Nos. 24 and 25 were killed after seven days on polished rice; Nos. 26 and 27, after eleven days; Nos. 28 and 29, after fourteen days; No. 30, after sixteen days; No. 31, after seventeen days; No. 32, after eighteen days; No. 33, after nineteen days; No. 35, after twenty-two, and No. 36, after twenty-three days on polished rice. None of these fowls showed symptoms of peripheral neuritis and, with the exception of Nos. 35 and 36 (somewhat droopy), all were lively and apparently normal. As controls 4 normal fowls were used. The mitochondria methods proved to be the most delicate and serviceable in this series, and the methods of Benda, Meves, Bensley, and Regaud were employed as checks on each other. It was found that after prolonged fixation in Müller's fluid (two weeks or more in 2 or 3 changes), each of the above methods gave excellent results. As the iron-

hæmatoxylin method (Meves, Regaud, Rubaschkin,(18) and others) gives the most permanent preparations and is easy of application, it was most frequently employed.[5]

In good preparations of a normal nerve stained by this and the other mitochondria methods, the medullary sheath is seen to contain innumerable little bacilli-like rods. When seen from above, the fiber gives the appearance of containing both rods and granules, but in a fiber which has been split down the middle in sectioning, so that the medullary sheath is seen only on either side of the axis cylinder and not above, only rods are to be observed. These rods arrange themselves in a general radial direction around the axis cylinder, but at places show a more or less X-like crossing. From this it is apparent that the granular appearance is due to an end view of the radially arranged rods. These appearances are identical to similar structures and arrangements described and illustrated by Nageotte(19) in the cauda equina of the guinea pig and termed by him mitochondria. Plate VII, fig. 14, is a photomicrograph of an iron-hæmatoxylin preparation, and illustrates the arrangement and number of these rods in a normal nerve. At *a*, *a'*, and *a''*, the radial arrangement of the rods is shown. This picture is typical of all preparations from the nerves of the 4 normal fowls stained by each of the mitochondria methods mentioned above.

Fowls 24 and 25, fed for seven days on polished rice, are the earliest on which examinations were made in this series. Fowls were not killed at an earlier period than this, because it was thought that several days must elapse before the normal metabolic balance of the fowl would be disturbed. Thus in these 2 fowls, which serve as a check on each other, we did not expect

[5] The iron-hæmatoxylin method for staining mitochondria is very simple, easy of application, and well adapted for nerve tissue. It has the further advantage of being permanent and it brings out the rods in sharp contrast. Small pieces are fixed and mordanted in Müller's fluid two weeks or longer, washed in water (twelve hours), and embedded in paraffine through xylol. Sections, not over 5 microns thick, are mordanted (twelve to twenty-four hours) in 2 per cent iron ammonia alum, washed in water, and stained in Weigert's hæmatoxylin (for myelin sheath), eight to twenty-four hours in this climate. Differentiate in iron ammonia alum (1 or 2 per cent). Sections sometimes give clearer pictures if immediately before staining they are treated one or two minutes in 0.25 per cent potassium permanganate, washed in water, and placed for one or two minutes in Pahl's solution of 0.5 per cent potassium sulphite and 0.5 per cent acid oxalic. For further details on staining mitochondria and other methods, see Altmann,(16) Bensley,(12) Benda,(14) Meves,(13) Regaud,(15) and Rubaschkin.(18)

to find any demonstrable change from the normal. Much to our surprise, however, nearly all the rods had disappeared from practically every fiber of the sciatic shown in a longitudinal section through the middle of the nerve. In the smallest fibers a few rods were to be seen, but they were extremely scarce in the large fibers. This condition obtained in the sciatic of both fowls. The stainable material of the medullary sheath which demonstrated itself in the form of rods in the normal fiber here took on quite a different and surprising appearance. In the 7-day fowls it was seen as smaller, or larger, irregular, branched, and anastomosing globules. A few fibers showed an apparent swelling here and there and a more or less distinct network. Plate VIII, fig. 15, is taken from the sciatic of fowl 24, and is more or less typical for both birds. The globular arrangement is well demonstrated—*b* is a fiber showing the swelling and network arrangement. This was confirmed by the other methods. This change in so short a time was so pronounced and remarkable that with a little skepticism the normal nerves were again worked over. These confirmed in every particular our first preparations. With considerable enthusiasm, the remainder of the series of fowls was examined, and a routine examination of all the previous fowls was begun. The results were well worth the trouble, for in none of these preparations was it possible to find a single fiber which even approached in appearance that of the normal fiber. It was the rarest instance that a single rod could be found.

Changes in the fibers from the remainder of the series (that is, fowls fed for more than seven days on polished rice) were not so pronounced over the 7-day preparations as this was over the normal. In fact the 11-day preparation resembles very closely the 7-day, and it is practically impossible to distinguish the 11- or 14-day from an 18-day preparation. Later changes are shown in Plate VIII, fig. 16, and Plate IX, fig. 17. In these latter subjects, most of the fibers show little advance over the 7-day or over the next preceding stage. There is, however, to be observed a general tendency toward segmentation of the myelin in the 11-day, 14-day, *et seq.* A few fibers here and there, on the other hand, show progressive change. The stainable substance collects in larger irregular globules and skeins, the remainder of the medullary sheath being remarkably clear. (Plate VIII, fig. 16, fibers *a*, *b*, *c*. *d*.) In fowls which have been fed for a longer period, a few fibers show a still more pronounced collection of the stainable material into large irregular masses and segments. Plate IX, fig. 17 *b*, is characteristic of such a fiber. The other and great

majority of the fibers show little or no advance over the preceding stage. In those fibers from fowls which present symptoms of neuritis and whose nerves show pronounced degeneration, the stainable material takes on a more diffuse and somewhat homogeneous appearance in a majority of the fibers. Other fibers are seen (10 to 15 per cent) which show an exaggeration of the globular arrangement. These globules are more regular in shape and oval in contour, and the stainable material shows a preference for the periphery. These resemble very much the fibers which show advanced degeneration by the Marchi method and are probably identical with them. (Plate IX, fig. 18, fiber *a*.) Thus it is evident that the fibers of the peripheral nerves of fowls on a polished rice diet show an early (7-day or somewhat earlier) change in their medullary sheath, and that in a varying percentage (10 to 15) this change is progressive and leads to the condition ordinarily termed degeneration. This can easily be followed in Plate VIII, figs. 15 and 16, and Plate IX, figs. 17 and 18.

IV. THE INFLUENCE OF VARIOUS ARTICLES OF FOOD ON THE PRODUCTION OF POLYNEURITIS GALLINARUM.

In pursuing investigations into the cause of beriberi it has been by no means uncommon to find instances in both experience and the literature where beriberi has developed in spite of the fact that the patients had received what was supposed to be a fairly well-balanced ration containing rice as the staple article of diet. This observation has been frequently urged as an insuperable objection to the theory that beriberi is caused by rice diet. In a previous paper (8) one of us has shown that fowls likewise develop polyneuritis when fed on diet containing a sufficiency of all the alimentary principles, provided no one of the ingredients of this diet contains the neuritis-preventing substance. It is apparent that the neuritis-preventing substance is not present in all articles of food, and that, in those articles in which it is present, it occurs in very variable amounts. It was, therefore, considered desirable to test certain articles that are usually included in an ordinary diet, in order to determine just what degree of protection they would afford when combined with a staple of polished rice.

The following experiments were performed for this purpose:

Experiment 29.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of raw potatoes. One fowl developed neuritis in thirty-two days, 1 in thirty-eight days, and the other 2 fowls remained well after sixty-three days, when the experiment was discontinued.

Experiment 30.—Four fowls were fed on polished rice, and in addition

were given daily 10 grams of boiled potatoes. One fowl developed neuritis after twenty-five days' feeding, 1 fowl developed neuritis after fifty-nine days, and 2 fowls remained well after sixty-three days, when the experiment was discontinued.

Experiment 31.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of white wheat bread such as is issued to troops. One fowl developed typical neuritis in twenty-six days, 1 in twenty-seven days, and 1 in thirty-two days. One fowl remained well after forty-eight days, when the experiment was discontinued.

Experiment 32.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of raw beef. One fowl developed neuritis in nineteen days, 1 in forty-eight days, and 1 in fifty-seven days, while 1 fowl remained well after sixty-three days, when the experiment was discontinued.

Experiment 33.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of boiled beef. One fowl developed neuritis in twenty-five days, while the other 3 fowls remained well after sixty-three days, when the experiment was discontinued.

Experiment 34.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of dried peas. All 4 fowls remained in perfect health when the experiment was discontinued after sixty-three days' feeding.

Experiment 35.—Four fowls were fed on polished rice, and in addition were given daily 5 cubic centimeters of canned milk (Highland Cream). One fowl developed neuritis in nineteen days, 1 in twenty-three days, and 1 in thirty-two days. One fowl remained well after sixty-three days' feeding.

Experiment 36.—Four fowls were fed on polished rice, and in addition were given daily 5 cubic centimeters of fresh cow's milk. One fowl developed neuritis in twenty-three days, 1 in thirty-one days, and 2 fowls remained well after sixty-three days.

Experiment 37.—Four fowls were fed on polished rice, and in addition were given daily 10 grams of unroasted peanuts. One fowl died of avian diphtheria after twenty-eight days' feeding without developing neuritis, and the other 3 fowls remained well after sixty days' feeding.

It should be noted that in all of these experiments the birds were fed these different articles of diet by hand, so that there can be no doubt as to what they actually received. It is a striking fact that the only two of these groups that received complete protection were those in which the fowls were given a daily addition of 10 grams of dried peas and 10 grams of peanuts.

V. SUMMARY.

1. There appear to be three types of polyneuritis gallinarum:

(a) A form in which the symptoms of neuritis and those of general prostration are combined. This is the usual form. When these birds are given an extract of rice polishing, they improve at once in general condition, but the symptoms of neuritis only disappear after several months of treatment.

(b) A form in which there is pronounced neuritis, but the fowl remains in good general health. These fowls will also recover from the neuritis after several months' treatment with the extract of rice polishings.

(c) A form described above as fulminating cases, in which the symptoms of neuritis are absent, but in which greater general prostration occurs. These fowls recover speedily when given extract of rice polishings.

2. In polyneuritis gallinarum developing after a prolonged diet of polished rice the heart may show no microscopic change. In other cases the heart may show slight œdema, a slight increase in pigment, or an appearance of beginning mucoid or parenchymatous degeneration.

3. While in marked cases of neuritis every fiber of the vagus may and usually does show degenerative changes, as indicated by the Marchi method, no fiber has been observed in which the change was far advanced. We have not been able to correlate the extent of degeneration in the vagus with the change in the heart nor with the severity of the symptoms before death.

4. No marked changes suggestive of degeneration have been observed in the cervical sympathetic ganglia nor in the post- or preganglionic fibers.

5. In every one of the 56 fowls which had been fed thirty-five days or more on polished rice, changes indicative of degeneration (Marchi method) were seen in the fibers of the sciatic nerve, regardless of whether symptoms of neuritis had or had not manifested themselves before death. (Plate II, fig. 3, and Plate XI, fig. 24.)

6. Advanced degeneration in the peripheral nerve fibers manifests itself by a change in both myelin sheath and in the axis cylinder. The myelin sheath breaks up into globules and droplets, which stain black in the Marchi solution—indicative of fatty degeneration. The axis cylinder breaks up into segments or disintegrates in all those fibers showing advanced degeneration in the medullary sheath. (Plate V, fig. 9.)

7. The degree of degeneration in the sciatic nerve corresponds closely with the extent of the paralysis of the legs. Advanced degeneration was observed in only 10 to 15 per cent of the fibers of the sciatic nerve of fowls showing pronounced symptoms of leg paralysis. In the remaining fibers the change was not advanced.

8. We could detect no difference in the degeneration in the sciatic and its peripheral branches either as regards extent or time of onset.

9. Degeneration was observed in both dorsal and ventral nerve roots, being most pronounced in the latter.

10. Degenerative changes in both axis cylinder and medullary sheath were seen in fibers of all columns of the thoracic spinal cord. (Plate V, fig. 10, Plate VI, figs. 11 and 12, Plate VII, fig. 13.)

11. Changes were observed (Nissl method) in certain large cells of both ventral and dorsal horns of the gray substance of the lumbosacral cord. In the cells of both horns, the tigroid bodies were not visible, and the stainable material was collected at one side of the cell around the base of one of the processes. Cells were occasionally seen whose nuclei stained very poorly. (Plate X, fig. 22.)

12. Mitochondria were observed in the nerve cells of the lumbosacral cord, even though there was a pronounced alteration of the tigroid bodies. The mitochondria here were of similar appearance and almost or quite as numerous as in corresponding cells of the normal cord.

13. In the medullary sheath of fibers of the sciatic nerve of normal fowls numerous small, bacilli-like rods, arranged radially around the axis cylinder, were made apparent by the various mitochondria methods. These structures are probably mitochondria. (Plate VII, fig. 14.)

14. Fowls show alteration in the medullary sheath of the sciatic fibers after only seven days on a polished rice diet. In the sciatic fibers of fowls fed for seven days on polished rice alone, the rods are scarcely to be observed. Instead, the stainable material shows remarkable alterations and occurs in the form of irregular, branched, and anastomosing masses. (Plate VIII, fig. 15.)

15. In fowls fed for a longer period, these masses show, in a certain percentage of the fibers, progressive changes which manifest themselves in the form of more definite skeins and segmentations and larger masses and globules of stainable material. In fibers showing marked degeneration by the Marchi method these occur as larger or smaller vesicular, oval globules and correspond to the black globules shown by the Marchi preparations. Plate VIII, fig. 16, and Plate IX, figs. 17 and 18 illustrate these changes.

16. When fowls are fed on polished rice and in addition given some protective substance, such as is contained in extract of rice polishings or in various foods, but in insufficient quantity to confer complete protection, the disease appears in its char-

acteristic form and with all the evidences of nerve degeneration, but after a prolonged incubation period—forty-five to ninety days, or even after one year of such feeding (Eijkman).

17. When fowls are fed on polished rice and in addition receive daily 10 grams of white wheat bread or 5 cubic centimeters of canned milk, they receive little or no protection from polyneuritis gallinarum.

18. When fowls are fed on polished rice and in addition receive daily 10 grams of meat cooked or uncooked, 10 grams of potatoes cooked or uncooked, or 5 cubic centimeters of fresh cow's milk, they receive partial protection as indicated by the prolongation of the incubation period.

19. When fowls are fed on polished rice and in addition receive daily 10 grams of dried peas or 10 grams of peanuts, they receive complete protection for at least sixty days.

VI. CONCLUSIONS AND DISCUSSION.

CONCLUSIONS.

1. In addition to the changes demonstrated above, Funk (22) has shown that chemical changes take place in the brains of fowls suffering from polyneuritis gallinarum. It therefore appears that the disease is not simply a peripheral neuritis as has been generally supposed. On the contrary, the entire nervous system is affected.

2. The symptoms of the disease are not chiefly referable to degeneration of the peripheral nerves, since the degeneration occurs before symptoms arise, and because advanced degeneration may be present accompanied by no symptoms at all, and because degeneration of the nerves remains after recovery has occurred.

DISCUSSION.

It is apparent from this study that the symptomatology and pathology of polyneuritis gallinarum can not be regarded as identical with that of beriberi in man. We have never observed any œdema in fowls at all comparable to wet beriberi in man, and while there are undoubtedly slight changes in the heart of fowls suffering from polyneuritis, there is none of the hypertrophy which is such a characteristic finding in human beriberi. In spite of these facts, however, there is more similarity than difference between the two diseases.

When we consider the etiology of the two diseases, the case is different. The experiments of Fraser and Stanton (23) and of

Strong and Crowell(24) prove beyond the shadow of a doubt that beriberi in man is the result of a too nearly exclusive diet of polished rice, or of other foods lacking in the neuritis-preventing substance. It has been proved beyond question that polyneuritis of fowls is due to a similar diet. The cause of the two diseases is therefore the same. Therefore, the conclusion already published by Chamberlain and Vedder(6) "that the two conditions are due to the same pathological process causing slightly different manifestations in diverse species" is abundantly justified. Since this is the case, it is evident that we may deduce some important facts concerning the relation between diet and beriberi from the above feeding experiments on fowls.

Both meat and potatoes contain a certain, but relatively small, amount of the neuritis-preventing substance. This explains the immunity from beriberi of those races whose main articles of diet are meat and potatoes. On the other hand, the man who eats a pound of polished rice daily with a small or occasional addition of meat will not receive complete protection from beriberi, although the onset of the disease may be delayed by the meat thus eaten. Eijkman showed that fowls fed entirely on potato starch did not develop polyneuritis. This confirms our observation that potatoes contain the neuritis-preventing substance. If men live chiefly on potatoes, as many Irish peasants have often done, they will be protected from beriberi, but a diet of polished rice with a small addition of potatoes would result in the production of beriberi.

Our observation that ordinary white bread is quite lacking in the neuritis-preventing substance is also interesting. This confirms the observation of Holst(25) that animals fed on wheat bread developed neuritis while those fed on rye bread did not. Beriberi began to appear on Norwegian sailing ships in 1894, when the diet of the sailors was changed. Prior to that date they ate largely rye bread. Subsequently they received wheat bread and developed beriberi. The occurrence of ship beriberi among sailors who live chiefly on bread or hardtack made of white or overmilled wheat flour is thus explained.

Little(26) has also recently reported the occurrence of beriberi in Labrador and Newfoundland among a native population living during certain seasons almost exclusively on white wheat flour. This has been taken in some quarters as throwing doubt upon the theory that beriberi is produced by a diet of polished rice. However, since polished rice only produces beriberi because of its deficiency in the neuritis-preventing substance and since

wheat flour is shown to be similarly deficient,[6] this observation is a strong confirmation of that theory. It is evident that we can not prevent beriberi by adding bread to the ration.

The experiments show that peas and peanuts possess the property of preventing the disease equally with beans or mongos (katjang idjo). It is probable that most leguminous seeds possess this property. This is of practical importance since it indicates that peas will be equally as efficacious as beans in preventing beriberi when added to a ration for use on shipboard or for natives subsisting chiefly upon rice.

It will be noted that both meat and potatoes when cooked appeared to afford more protection than when eaten raw. It had been expected that the reverse would be the case, since it was supposed that some of the protective substance might be destroyed by cooking. We are at present unable to account for the fact that the cooked food appeared to afford greater protection than raw food. These experiments, however, dispose of the objection so often raised against the deficiency theory that men who eat various quantities of other food in addition to the staple diet of rice may nevertheless develop beriberi. It is clearly shown that most articles of diet contain only small amounts of the protective substance, and that when even moderate quantities of many foods are added to a staple of rice, which practically contains none at all, the deficiency still exists.

Funk(27) has apparently isolated the neuritis-preventing substance from rice polishings and other foodstuffs, and has shown that it is an organic base probably belonging to the pyramidine group having a formula of $C_{17}H_{20}N_2O_7$ and a melting point of 233° C. This base, or vitamine as Funk calls it, was precipitated by phosphotungstic acid. Chamberlain, Vedder, and Williams(7) had already tried this method unsuccessfully, but they do not regard their failure as disproving Funk's results, owing to the fact that their extract was prepared in a slightly different manner from that used by Funk.

Accepting Funk's discovery as correct, from the above conclusions we deduce the following: The organic base or vitamine, which prevents the development of polyneuritis gallinarum and which is present in varying amounts in different foodstuffs, is a building stone which is essential for the normal metabolism

[6] Little also showed that the disease in Labrador could be prevented and cured by the use of bran or polishings from wheat, thus clearly demonstrating that the disease in this case was also due to a food deficiency.

of nervous tissue. Moreover, a certain amount of this vitamine is necessary for each fowl constantly as is shown by the fact that degeneration of the nerves may be demonstrated within seven days after the supply of this vitamine is cut down by a polished rice diet. The amount necessary, however, varies for different fowls according to their individual idiosyncrasy, because, as has been shown, some fowls are more susceptible to this deficiency than others. If the supply of vitamine is cut down by feeding on polished rice, or any other dietary which contains an insufficient amount of this substance, the normal metabolism of the nervous system at once suffers. Should this faulty diet be continued, the degeneration of the nervous system progresses steadily, until a point is finally reached when the symptoms of polyneuritis appear. Even though the amount of this necessary substance is reduced only very slightly below the quantity essential for a given fowl, degeneration occurs though more slowly, and the symptoms of neuritis will appear if the reduction be continued for a sufficient length of time.

The question naturally arises if this vitamine is essential to normal nervous metabolism, why are any fowls on a polished rice diet protected from polyneuritis gallinarum and any men from beriberi? This is probably due to the fact that the metabolic processes are much more active in some individuals than in others. Those fowls whose metabolic processes are very active require larger amounts of vitamine, and succumb most promptly on a diet of polished rice. In those fowls whose metabolic processes are more sluggish, the incubation period is longer. It is probable that even polished rice contains a trifling quantity of this vitamine in comparison with other food. Therefore, some fowls whose metabolism is exceptionally sluggish may be able to subsist for some time on this polished rice without developing neuritis. However, in most cases this protection is not complete as is shown by the fact that degeneration may be demonstrated in their nerves, although they are apparently in good health. Probably in most instances the protection apparently enjoyed by some fowls on polished rice is only partial, and if the diet be continued long enough practically all will succumb. The interesting case related by Eijkman where the fowl developed neuritis only after a year's feeding is a case in point. The same explanation will account for the fact that some men are more susceptible to beriberi than others and that some are apparently exempt. From the fact that the incubation period in man averages three or four months as compared with only twenty-six days in the fowl,

we may infer that the amount of vitamine required by man is much less proportionately than that required by the fowl.

The question of loss of weight also requires some elucidation. It is quite apparent that if the metabolism of the entire nervous system suffers from the loss of this vitamine, the rest of the body tissues will also waste away as a result and there will be great loss of weight. But how account for the loss of weight that occurs in fowls fed on polished rice, but which have received this substance in extract of rice polishings? It is believed that the loss of weight in these cases may be due to the fact that the fowl living on this diet is not in equilibrium of metabolism with regard to other substances. For instance, it is quite possible that it is suffering from a deficiency of fat, of phosphorus, of potassium, and of other substances that are deficient in polished rice. This is quite enough to account for the loss of weight in these cases.

The cause of the great prostration in this disease should also be considered. Some birds present this symptom while others do not. We have seen that the degree of degeneration of the vagus bears no relation to the degree of prostration of the fowl, and that there is not sufficient change in the heart to account for the sudden death. It is highly improbable that the prostration is due to the peripheral neuritis. There are several possible explanations of this phenomenon. Since the entire nervous system is probably affected in this disease, we can easily suppose that this general prostration occurs when the higher nerve centers either in the brain or the cord are affected by the degenerative process.

On the other hand, a most attractive hypothesis presents itself to account for this condition. Let us suppose that rice polishings and other foods contain two substances or vitamines that are essential for proper metabolism. One of these is the neuritis-preventing substance, and the other a substance that prevents general prostration, cardiac failure, etc. This hypothesis would account for the three classes of symptoms observed in fowls suffering from polyneuritis. Those cases belonging to class 1 evidently suffer from the deprivation of both vitamines. The cases in class 2 suffer from deprivation of the neuritis-preventing vitamine, but have received sufficient of the second vitamine to prevent the occurrence of prostration; while those fowls in class 3 have received sufficient of the neuritis-preventing vitamine to defer at least the symptoms of nerve degeneration, but not enough of the second vitamine to prevent their dying of general prostration. This supposition would account for the three types

of beriberi in the same way. It would also offer a rational explanation for the confusing fact observed in ship beriberi, that neuritis is sometimes apparently entirely absent, and is usually slight, while in other cases the neuritis is pronounced. On account of this fact, many observers such as Nocht have not been willing to accept ship beriberi as true beriberi. If this explanation were correct, this difficulty would disappear, for it would evidently be possible for the symptoms of wet beriberi and the symptoms of polyneuritis to be mixed in all sorts of forms depending upon the proportions of these two essential vitamines that were present in the diet consumed in each case. Moreover, this hypothesis might account for the existence of the disease epidemic dropsy which some observers have thought to be a form of beriberi while others have denied this. Epidemic dropsy according to this theory would be caused by the lack of this second vitamine. There are many indications that this hypothesis may be the correct one, but at present experimental evidence is lacking to prove its validity. Experiments are being continued by Vedder and Williams.

The degeneration found in the cord presents another field for speculation. It is generally believed by physiologists that the fibers of the cord are incapable of regeneration. Yet here we have an instance where degeneration has undoubtedly occurred and where apparently complete recovery also takes place. Can this recovery occur without regeneration of these fibers of the cord by the process of training other fibers to assume the function of those that have been destroyed, or does regeneration of these fibers actually occur?

In order to study regeneration of the nerves, several fowls suffering from pronounced polyneuritis were saved by administration of extract of rice polishings. It was observed that after a few days a pronounced spasticity, similar to that observed when the symptoms of neuritis were first manifested and described above, set in. This spastic condition remained for two months after daily administration of extract of rice polishings was commenced, without apparent improvement. *It then suddenly disappeared in a single day.* On one day, the fowl was hardly able to totter about on its toes, and on the next day it was walking about like a normal fowl. Nor was this an isolated observation. Two questions are suggested. What is the cause of this spasticity, and what causes it to disappear suddenly? In this connection we may recollect that the symptoms of paralysis also often appeared in a single day, although the degeneration of the nerves

was very gradual. The sudden appearance of the paralysis and the immediate cures reported by Funk after administration of the vitamine could be explained if this vitamine constitutes an essential element for the metabolism of the nerve cells. The changes found by us in the nerve cells of the cord appear to lend support to this view. These changes are probably not a true degeneration, since similar changes have been observed in nerve cells after fatigue. The paralysis, therefore, may appear suddenly when the nerve cells become exhausted from the lack of this vitamine essential to their metabolism, and disappear equally promptly when this substance is supplied in sufficient quantity.

A definite answer to all of these questions is manifestly beyond the scope of this paper. However, the questions which have been raised by this study make it certain that this interesting disease of fowls deserves further investigation, and we may expect our knowledge of the metabolism and pathology of the nervous system to be greatly extended by such work.

REFERENCES.

(1) Eijkman. Eine beriberiähnliche Krankheit *Virchow's Arch.* (1897), 168, 523.
(2) Maurer. Polyneuritis der Hühner und Beriberi. *Münch. Med. Wochenschr.* (1907), 54, 131.
(3) Fraser and Stanton. The etiology of beriberi. Studies from Institute for Medical Research. Federated Malay States (1911), No. 12.
(4) Shiga and Kusama. Über die kakke- (beriberi-) ähnliche Krankheit der Tiere. *Beihefte z. Arch. f. Schiffs- u. Trop.-Hyg.* (1911), 15, 59.
(5) Chamberlain and Vedder. A contribution to the etiology of beriberi. *Phil. Journ. Sci.* (1911), 6, 251.
(6) Idem. A second contribution to the etiology of beriberi. *Ibid.* (1911), 6, 395.
(7) Chamberlain, Vedder, and Williams. A third contribution to the etiology of beriberi. *Ibid.* (1912), 7, 39.
(8) Vedder. A fourth contribution to the etiology of beriberi. *Ibid.* (1912), 7, 415.
(9) Engelmann. *Pflüger's Arch.* (1876) 13, 474.
(10) Monakow. Cited by Obersteiner. The anatomy of the central nervous organs. Translated by Alexander Hill. London (1900), 139.
(11) Nissl. *Centralbl. f. Nervenh. u. Psychiat.* (1894), 17, 337; *Neurol. Centralbl.* (1896), 15, 9.
(12) Bensley. *Am. Journ. Anat.* (1911), 12, 297.
(13) Meves. *Arch. f. mikros. Anat. u. Entw.* (1908), 71, 573.
(14) Benda. Verh. der Anat. Gesellsch. Bonn (1901).
(15) Regaud. *Compt. rend Soc. biol.* (1908), 65, 660.
(16) Altmann. Die Elementarorganismen und ihre Beziehungen zu den Zellen. 2. Auflage. Leipzig (1894).

(17) COWDRY. *Anat. Record.* (1912), 6, 33.
(18) RUBASCHKIN. *Anat. Hefte.* 1st Abt. (1910), 41, 399.
(19) NAGEOTTE. *Arch. f. mikros. Anat.* Abt. 1 (1911), 77, 245.
(20) MANN. *Journ. Anat. & Phys.* (1895), 29, 100.
(21) HODGE. *Journ. Morph.* (1892), 7, 1.
(22) FUNK. The effect of a diet of polished rice on the nitrogen and phosphorus of the brain. *Journ. Physiol.* (1912), 44, 50.
(23) FRASER AND STANTON. Studies from Institute for Medical Research. Federated Malay States (1909), No. 10; *Lancet* (1909), 1, 451.
(24) STRONG AND CROWELL. *Phil. Journ. Sci.* (1912), 7, 271.
(25) HOLST. *Trans. Soc. Trop. Med. & Hyg.* (1911), 5, 76.
(26) LITTLE. Beriberi caused by fine white flour. *Journ. Am. Med. Assoc.* (1912), 58, 2029.
(27) FUNK. The preparation from yeast and certain foodstuffs of the substance the deficiency of which in diet occasions polyneuritis in birds. *Journ. Physiol.* (1912), 45, 75.

ILLUSTRATIONS.

Photomicrographs by Martin and Cortes. Camera lucida outlines were used in the preparation of all the drawings.

PLATE I.

FIG. 1. Photomicrograph of a teased preparation of sciatic nerve from a normal fowl. (Marchi method.) Zeiss 4 × 4 mm.

2. Transverse section of lateral fiber column of thoracic spinal cord of normal fowl. (Marchi method.) At (*a*) blackened masses are seen in close proximity to the fibers. At (*b*) the black globules appear to be within the fiber.

PLATE II.

FIG. 3. Photomicrograph of a teased preparation of the sciatic nerve of fowl 6. (Marchi method.) For two days this fowl had been unable to stand, but appeared to be in good condition otherwise. Different stages of degeneration are here illustrated. Note occasional globules of degenerated myelin in some fibers (*a*), a diffuse blackening of the medullary sheath with indications of segmentation in fiber (*b*), and large globules of degenerated myelin in fiber (*c*). Zeiss 4 × 4 mm.

4. Fiber from sciatic nerve of fowl 6, showing advanced degeneration. (Marchi method.) Note large globules and small droplets of degenerated myelin and clear spaces between. The neurilemma sheath is well shown. Zeiss 4 × 4 mm.

PLATE III.

FIG. 5. Teased preparation of vagus of fowl 13 (good general condition, but unable to walk since three days). (Marchi method.) This figure shows relatively advanced degeneration (for our series). Numerous large globules of degenerated myelin are seen here and there. At the periphery where the individual fibers are best seen, globules are to be observed at frequent intervals in every fiber. Zeiss 4 × AA.

6. High-power magnification of an area of the same preparation.

PLATE IV.

FIG. 7. Drawing of a nerve fiber from the sciatic to show early stage of myelin degeneration. (Marchi method.) Note diffuse blackening, tendency to segmentation (*s*), and beginning globular arrangement of the myelin (*G*); (*n*) is nucleus of neurilemma sheath. Zeiss 4 × 4 mm. Apochomatic (?).

8. From a transverse section of a sciatic nerve showing marked degeneration, to illustrate the percentage of fibers showing varying degrees of degeneration in a given plane. A majority of the fibers show blackening to some extent. *a*, *b*, *c*. etc., are cross sections of the larger globules of degenerated myelin. Zeiss 2 × 4 mm. Apochomatic.

PLATE V.

FIG. 9. Advanced degeneration in a nerve fiber from the sciatic, showing also segmentation of the axis cylinder. Swelling of the medullary sheath and the granular appearance of the axis cylinder are well shown: *a*, axis cylinder; *n*, node of Ranvier. Hæmatoxylin and acid fuchsin. Zeiss 3 × 1/12 oil immersion. Reduced one-half.

10. Cross section of fibers of the ventromarginal column of the thoracic cord from fowl 14, showing pronounced symptoms of peripheral neuritis and marked degeneration in the sciatic nerve. At *a* and *a'* two fibers are seen in which the axis cylinder has undergone fragmentation and granulation. Hæmatoxylin and acid fuchsin. Zeiss 4 × 1/12 oil immersion.

23. Fiber from the ventral portion of the midbrain of fowl 72 with pronounced neuritis. Small globules of degenerated myelin are clearly seen. Marchi method. Leitz 3 × 6.

PLATE VI.

FIG. 11. Transverse section of the posterior columns of the thoracic cord of fowl 14, showing pronounced symptoms of peripheral neuritis and marked degeneration in the sciatic. At *a*, *a'* and *a''*, three fibers are seen which undoubtedly contain globules of degenerated myelin. Marchi method. Zeiss 4 × AA. apr.

12. High-power illustration of same preparation as fig. 11—dorsomarginal (Gall's) column. Degenerated areas within the fibers are clearly seen at *a* and *a'*. Marchi method. Zeiss 4 × 4 aper.

PLATE VII.

FIG. 13. Longitudinal section of lateral column of thoracic cord of fowl 15, showing pronounced symptoms of peripheral neuritis and marked degeneration in the sciatic nerve. At *a*, *a'*, *a''*, and *a'''*, fibers are seen containing globules and droplets of degenerated myelin. Marchi method. Zeiss 4 × AA. aper.

14. Longitudinal section of the sciatic nerve of a normal fowl stained by the mitochondria (iron-hæmatoxylin) method. The stainable substance is seen in the form of little rods arranged radially around the axis cylinder. Note fibers *a*, *a'*, and *a''*. At *a* the rods show a tendency to cross. Zeiss 4 × 4 aper.

PLATE VIII.

FIG. 15. Longitudinal section of the sciatic nerve of a fowl fed for seven days on polished rice to illustrate the changes in the medullary sheath. The stainable substance is seen as larger or smaller irregular and branched masses. In fiber *b* a network formation is seen. Mitochondria (iron-hæmatoxylin) method. Zeiss 4 × 4 aper.

16. Same, from a fowl fed for eleven days on polished rice. The segmentation is a little more pronounced and in some fibers the masses are larger. Note fibers *a*, *b*, *c*, and *d*. Zeiss 4 × 4 mm. aper.

PLATE IX.

17. Longitudinal section of the sciatic nerve of a fowl fed for eighteen days on polished rice. In fiber *b*, the stainable material has collected into larger masses which in places coalesce into globules, *b*. Mitochondria (iron-hæmatoxylin) method. Zeiss 4 × 4 mm. aper.

18. Longitudinal section of the sciatic nerve of fowl 14, showing pronounced symptoms of peripheral neuritis and marked degeneration in the sciatic. Globules are more discreet than in fig. 17, and the stainable material is for the most part at the contoured periphery of the globules, *a*. The other fibers show a diffusion of the stainable material. Mitochondria (iron-hæmatoxylin) method. Zeiss 4 × 4 mm. aper.

PLATE X.

19. Nerve cell from spinal cord of normal fowl. Nissl stain. Zeiss 4 × 4 mm.

20. Same. Giemsa blood stain.

21. Nerve cell from ventrolateral group of the lumbosacral cord of a fowl (No. 48, twenty-four days on polished rice) with marked paralysis of the legs and marked degeneration in the sciatic. The tigroid bodies are no longer apparent. The stainable material which appears granular has collected at one side of the cell around the implantation cone (*a*) of the axis cylinder. Giemsa blood stain. Zeiss 4 × D.

22. Nerve cell from same preparation as fig. 21, same group. Note bulging of cell at *a* where the stainable material is collected in one mass. The nucleus, *n*, shows degenerative changes. Zeiss 4 × 1/12 oil immersion. Camera lucida, reduced ½.

PLATE XI.

24. Teased preparation (Marchi method) of the sciatic nerve of fowl 16 which was fed for thirty-five days on polished rice without showing any symptoms of neuritis. At *a*, a fiber is seen showing advanced degeneration. Other fibers show less marked change. Zeiss 4 × 4 mm.

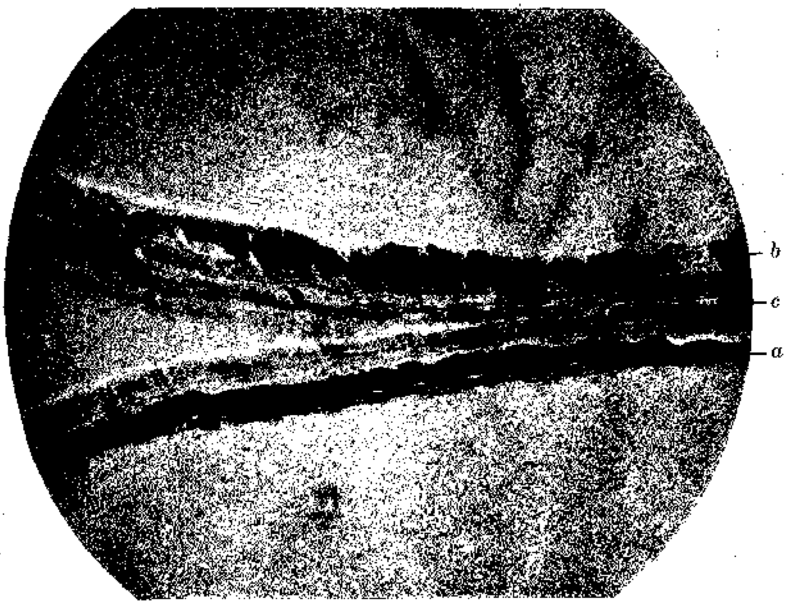

Fig. 3.

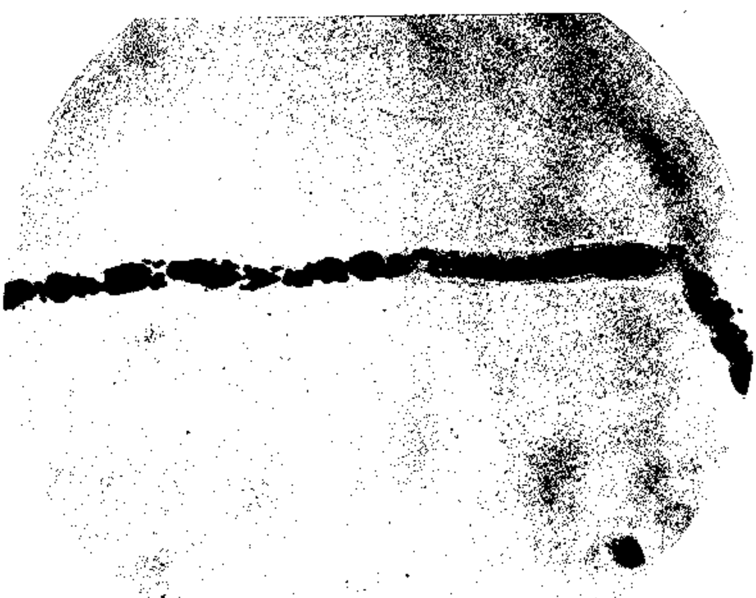

Fig. 4.

PLATE II.

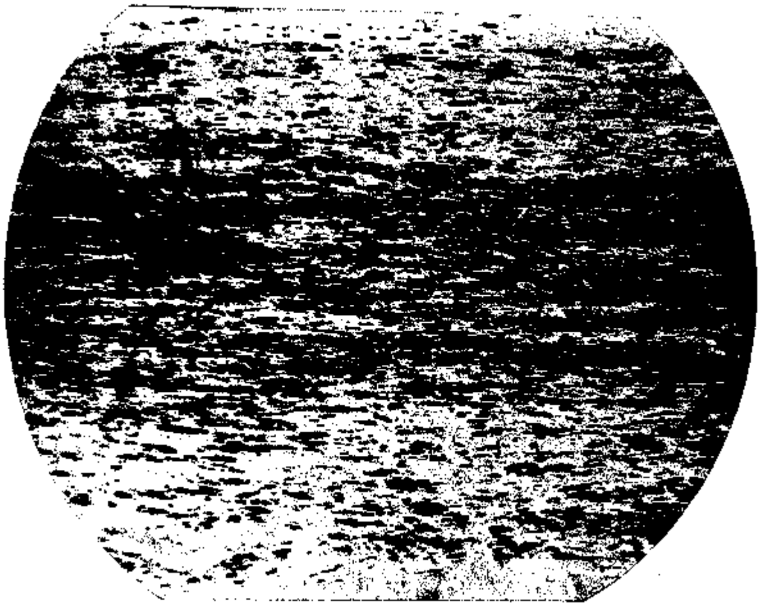

Fig. 5.

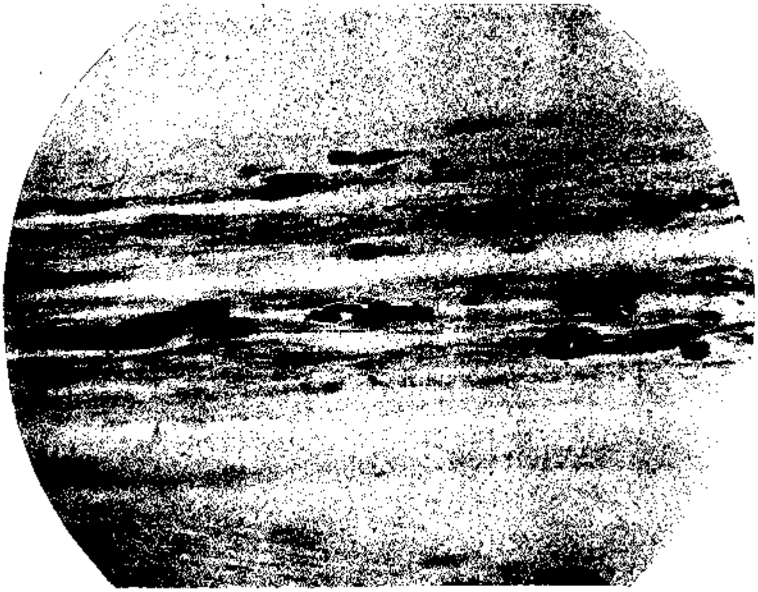

Fig. 6.

PLATE III.

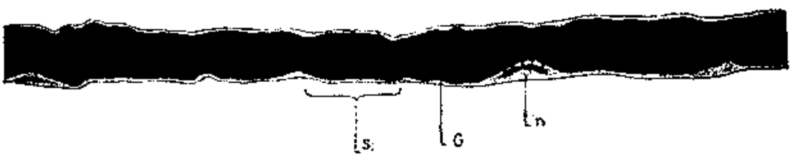

Fig. 7.

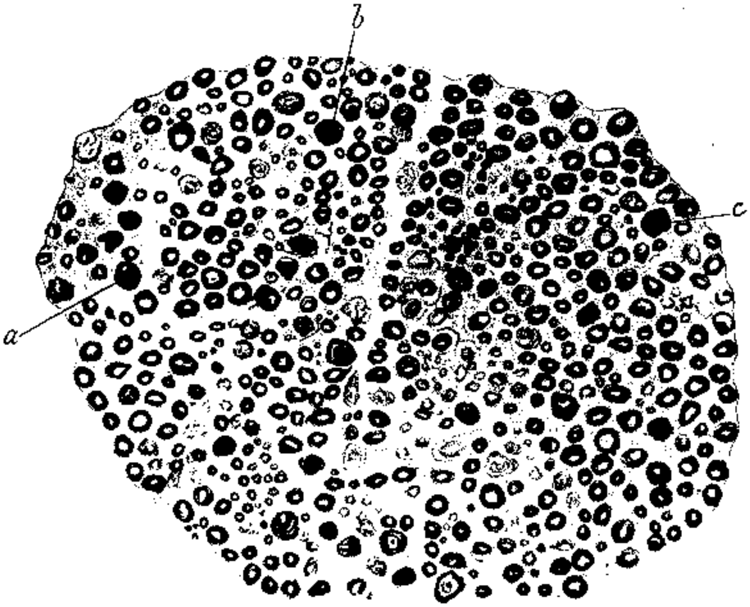

Fig. 8.

PLATE IV.

FIG. 9.

FIG. 23.

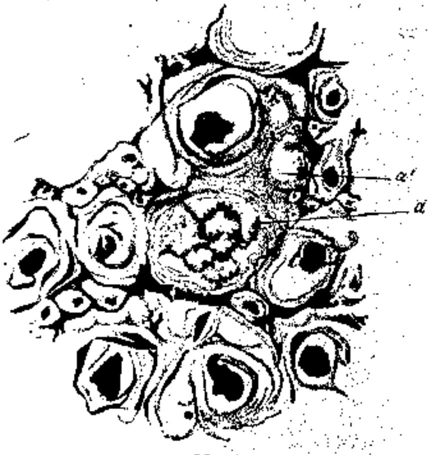

FIG. 10.

PLATE V.

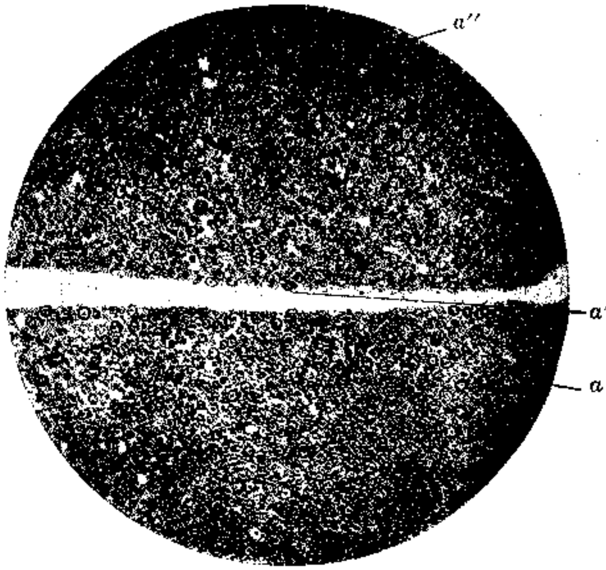

Fig. 11.

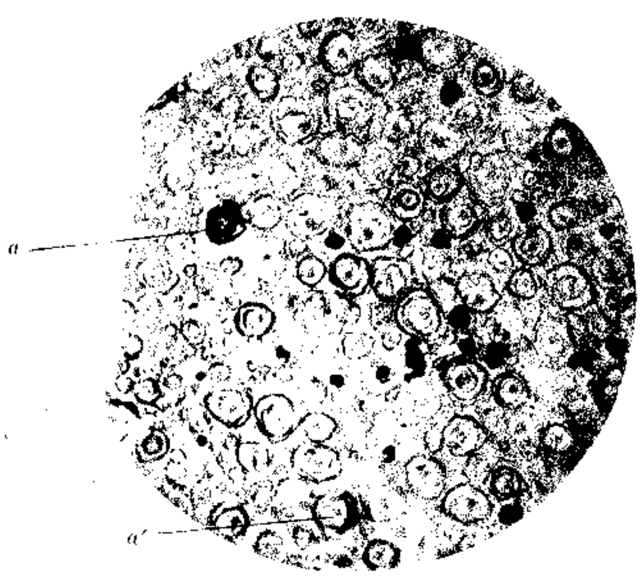

Fig. 12.

PLATE VI.

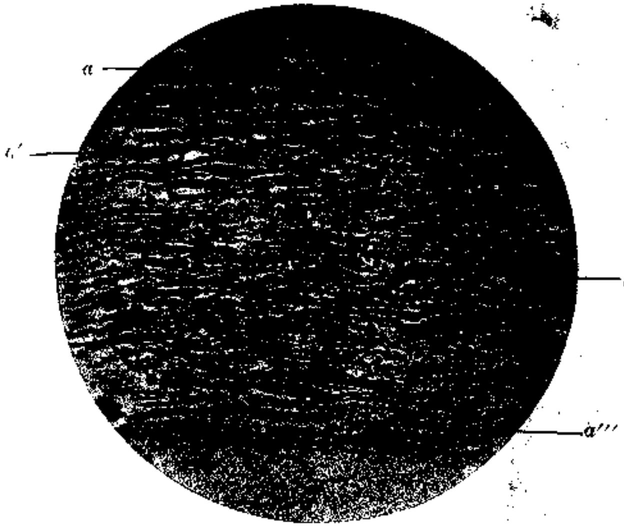

Fig. 13.

Fig. 14.

PLATE VII.

The definitions, while concise, are comprehensive, and the correct pronunciation, the capitalization, and the derivation of the words are given. By the use of thin but opaque paper and small but clear-cut type, compactness is secured without sacrificing completeness or legibility, while reference is facilitated by printing the words in heavy type and making them project beyond the line of the paragraph. The work is supplemented by many anatomical, clinical, posological, and therapeutical tables and by a large number of good plates, many of which are colored. The book is well and attractively bound in limp red leather.

E. L. W.

Contributions to Medical Science by Howard Taylor Ricketts 1870–1910. Published as a Tribute to his Memory by his Colleagues under the Auspices of the Chicago Pathological Society. The University of Chicago Press. Chicago, Illinois. 1911. Pp. 497. Cloth.

This volume, in which are collected all of the original papers of investigations published by Doctor Ricketts and his pupils, forms a worthy memorial to this brillant young man who had accomplished so much, who gave such promise for the future, and who sacrificed his life to science. A statement by the Committee of the Chicago Pathological Society appointed to prepare a suitable memorial and a short biography of Doctor Ricketts by Ludvig Hektoen forms a suitable introduction to the volume. The earlier papers on blastomycosis and imamunology are important contributions to medical science, but it is the work on Rocky Mountain spotted fever and typhus fever that established the reputation of Doctor Ricketts as a brilliant investigator. Rocky Mountain spotted fever was a disease of unknown etiology which occurs in certain regions of Montana and adjacent states and which was supposed to be communicated to man by the bite of a tick. Doctor Ricketts concluded that this disease is caused by a small bacillus which he was unable to cultivate on artificial media and which is transmitted from man to man by the bite of a tick, *Dermacentor occidentalis*, occurring in the region where this disease is endemic. He further proved that there is a hereditary transmission of the specific microörganism from tick to its offspring through the egg. These discoveries, if substantiated, are not only of importance as elucidating the etiology and epidemiology of the disease under consideration, but they disclosed new biological principles that promise to be of great significance to medicine. Hitherto it had been believed that only protozoan and spirochæte diseases were transmitted by ticks

and that only such diseases were capable of passing from the adult invertebrate host to offspring through infected eggs. Doctor Ricketts has shown that both of these processes can occur in bacterial diseases. How important these new biological facts may prove to be is indicated by Doctor Ricketts' subsequent investigations of typhus fever. The similarity of typhus fever, in some respects, to Rocky Mountain spotted fever led him to undertake the study of the former disease in Mexico. It was during this investigation that Doctor Ricketts fell a victim to the disease and died at Mexico City of typhus fever on May 3, 1910. It is a source of satisfaction to know that the sacrifice was not in vain. Before succumbing to the disease, he discovered, as in Rocky Mountain spotted fever, a small bacillus which could not be cultivated upon artificial media, which is probably that etiologic agent in typhus fever, and which appears to be transmitted from man to man by the bites of the body louse, *Pediculus vestimenti*.

E. L. W.

Manual of Practical Physiology. Designed for the Physiological Laboratory Course in the Curriculum of the American Association of Medical Colleges. By John C. Hemmeter, M. D., Ph. D., LL. D. With 55 illustrations. Philadelphia, P. Blakiston's Son & Co., 1012 Walnut Street. 1912. Pp. i–xxii+1–223. Price $2.50.

One is favorably impressed on first opening this book. The paper, type, and illustrations are good. The preface, but for a passage or two, might lead the reader to expect an improvement over the older manuals. Disappointment, however, begins with the first page of the book proper and increases as one reads further. The directions lack in definiteness, are wordy, and condescending. They contain irrelevant facts and irrelevant discussions, they dwell on nonessentials, new matter is introduced inopportunely, and inaccuracies abound. One or two quotations will give an impression of the inaccuracy of thought and of expression that pervades the book. On page seven, after the statement of the equation for the strength of the electric current, we read: "A simple example (presumably of the "electric current") is the flow of water through a nozzle of a syringe." And after speaking further about the syringe we find this: "Now if the nozzle of the syringe is longer (pressure same) less H_2O would flow, or if the hole in the nozzle is made smaller the same would happen, because in both cases resistance is increased. Applying this to the electrical circuit we learn that the longer

or thinner the conductor the greater the resistance and the less the flow of current." Thus endeth the discussion on "Electrical Measurements." This fault of inaccuracy, glaring as it is, is of minor importance, however, compared with another fault which mars the book. Instead of presenting the data obtained from the experiments in such a way as to lead the student to reason on the facts presented and so to develop the scientific attitude and habit of thought, the author presents to the student the conclusions ready made, and thus anticipates and forestalls all independent thought, making scientific training impossible.

A. O. SHAKLEE.

Veterinary Bacteriology. A Treatise on the Bacteria, Yeasts, Molds, and Protozoa Pathogenic for Domestic Animals. By Robert Earle Buchanan, Ph. D. With 214 illustrations. Philadelphia and London, W. B. Saunders Company. 1911.

In view of the scope of a work of this character it is quite impossible for a man of average training in the subject to pass a critical judgment upon the accuracy of all phases of the subject matter. In glancing through a book for this purpose one naturally pauses at the topics with which one feels especially familiar and subjects the statements of the author to scrutiny. Judged by such a method, the book is satisfactory and up to date with few exceptions.

The space devoted to Von Pirquet's cutaneous tuberculin reaction might better have been allotted to a discussion of the intradermal test for tuberculosis in cattle as described by Moussu and Mantoux. Their work was confirmed by Ward and Baker in a paper published in the Proceedings of the American Veterinary Medical Association for 1910 and in the American Veterinary Review for November, 1910, page 184. It is hoped that by the time the book is revised the intradermal test will have won more general recognition.

A review is not quite complete without a criticism of the use of at least one word. With all humility for my own shortcomings it is pointed out that the author uses the word epidemic instead of epizoötic on page 302. On the same line Dr. Brimhall's identity is masked by an unfortunate typographical error. Elsewhere the spelling of Johne is distorted by the addition of s.

In discussing antirinderpest serum the author accepts, as have many others, the statement of Kolle and Turner that "An injection of 50 to 100 cubic centimeters of the serum so secured will protect an animal against infection for a space of from 2 to 4

months usually." The accuracy of the experimental work upon which the foregoing statement is based seems not to have been challenged until the publication of Holmes' work in No. 1 of the Indian Civil Veterinary Department Memoirs, page 72. Holmes considers that serum alone will protect against the inoculated virus for about two weeks only. The present writer, on the basis of experiments, the results of which have not yet been published, is prepared to state that serum exerts no protection whatever against invasion by rinderpest virus.

The discussion of the nature of the virus of contagious pleuropneumonia would have been improved by reference to the work of Bordet, Borre, and others, appearing in the Annales de l'Institut Pasteur (1910), 25, No. 3.

A. R. WARD.

A Manual of Surgery for Students and Physicians. By Francis T. Stewart, M. D. Second edition with 553 illustrations. Philadelphia, P. Blakiston's Son & Co., 1012 Walnut Street. 1911. Pp. i–xi+1–682. Price $4.

This book contains the principles of surgery briefly and concisely stated. The manual has 31 chapters in which all the different diseases are considered separately. In the index, the most important references are placed first. It contains 553 illustrations, all of which are fairly demonstrative. In considering each disease, and particularly those sections dealing with diagnosis and treatment, the author has summarized as concisely as possible all of the various treatises on surgery for the student, physician, or general practitioner. This is very comprehensive and helpful, and it avoids loss of time for the reader. In a word, it is a useful book with clear style and logical and scientific arrangement.

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